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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/470,859	12/23/99	SARGENT R	A-68342-1/RM

HM12/0205
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EXAMINER	
CROUCH, D	
ART UNIT	**PAPER NUMBER**
1632	8

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/470,859	Sargent et al
Examiner	**Group Art Unit**
Deborah Crouch	1632

☒ Responsive to communication(s) filed on *Nov. 9, 2000*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three (3)* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-40* is/are pending in the applicat

Of the above, claim(s) *39* is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-38 and 40* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *3*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

Applicant's election without traverse of group I, claims 1-38 and 40 in Paper No. 7 is acknowledged.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-38 and 40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods comprising altering a chromosomal sequence of a nucleus by introducing a pair of single stranded targeting DNA segments associated with a recombinase into said donor nucleus, wherein said targeting DNA segments are homologous to each other and each comprising a homology clamp that is homologous to a targeted DNA sequence of said nucleus to provide a modified nucleus; inserting the modified nucleus into an enucleated oocyte to form a reconstituted oocyte and activating the oocyte to form a zygote, does not reasonably provide enablement for claims of record. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are drawn to methods of altering chromosomal sequence in a cell by introducing into a cell a targeting polynucleotides and a recombinase; and methods of altering a chromosomal sequence in an oocyte and/or sperm by introducing to an oocyte, a sperm, targeting polynucleotides and a recombinase and methods of altering a mitochondria chromosomal sequence by introducing into a cell a pair of single stranded targeting polynucleotides. The claims are not enabled as there is no evidence of record that while the targeting event may occur, that the altered chromosomal sequence of either a nucleus, an oocyte, sperm, or a mitochondria will produce zygote or transgenic offspring such that the phenotype which results from the altered chromosomal sequence will appear in the zygote or the offspring. It is noted that specification states that the claimed methods enhance the rate and efficiency of homologous recombination via the recombinase, and that as an enhancement, the rates of transgenesis in known methodologies such as nuclear chromosomal recombination, a sperm delivery of transgenes and

mitochondrial chromosomal recombination will improve (pages 1-3, especially page 2, lines 15-30). However, there is no evidence of record that the claimed methods will actually improve the result of transgenic animal production such that there is enhancement of the production of transgenic animals that have a desired phenotype. If the animal has no desired phenotype, then the method has no patentable use. In addition, there is no guidance in the specification as to the specific transformation of mitochondria. The mitochondrial membrane is materially different from either that of the cell or the nucleus. While the mitochondria certainly has its own genome, there are no protocols in the specification as to the means to introduce foreign DNA of interest into them.

As for the claims as whole, the specification, while describing methods of generating transgenic mice from the nuclei of cells that have been transformed with targeting DNA segments complexed with a recombinase, there is no evidence that the methodology ever resulted transgenic mice that a phenotype associated with the targeting method. For various metabolic pathways, it is well known that targeting one gene may not result in the production of an animal a defective associated with the mutation introduced as another metabolic pathway provided for the function targeted. Further, according to table 1, page 41, the specific examples are on relevant for the insertion of new restriction enzyme sites in the nuclear genome. Thus, for the breadth of applicant's claims the invention is not seen as enabled. The skilled artisan at the time of filing would have needed to perform an undue amount of experimentation without a predictable degree of success to implement the invention as claimed.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Campbell et al (1996) Nature 380, 64-66 or Cibelli et al (1998) Science 280, 1256-1258 in view of U.S. Patent 5,763,240 issued June 9, 1998 (Zarling et al).

Campbell et al teaches the production of sheep by nuclear transfer where the nuclear donor is an embryonic cell (page 64, table 1). Cibelli et al teaches the production of bovines by nuclear transfer where the donor nuclei is a fetal fibroblast (page 1258, col. 2, footnote 12). Both Campbell et al and Cibelli et al teach a nuclear transfer method where the donor nucleus is transplanted into an enucleated oocyte, where the zygote is activated, where the activated zygote is transferred to a surrogate mother for development of a term animal (*Ibid.*). Campbell et al teach the transfer of an embryo derived epithelial cell into an enucleated metaphase II oocyte, where the oocyte-cell couplet was electrofused and the oocyte activated 4-6 hours after transfer (page 64, Table 1). Cibelli et al teach transfer of a fibroblast nucleus into a metaphase II arrested enucleated oocyte, electrofusion of the oocyte-nucleus couplet and activation by a calcium ionophore and 6-dimethylaminopurine 2-4 hours after fusion (page 1258, col. 2, footnote 12). However, neither Campbell or Cibelli teach methods of producing transgenic sheep or bovines. Zarling et al teaches the production of transformed cells in culture by a method where DNA segments that are homologous to a target sequence, but contain a mutation of interested are first coated with a recombinase and second introduced to the target cell (col. 5, lines 54-63). Zarling et al teach that E. coli RecA or a recA-like protein can be the recombinases used to coat the targeting nucleotides (col. 11, lines 54-57). Rad51 is a mammalian function equivalent of RecA and known in the art at the time of filing. Given the teachings of Campbell et al and Cibelli et al, any cell type would be expected to provide a donor nucleus for nuclear transfer procedures. Thus at the time of the instant invention, it would have been obvious to the ordinary artisan to perform nuclear transfer procedures such as those taught by Campbell et al and Cibelli et al using as donor nuclei, nuclei that had undergone homologous recombination as taught by Zarling et al.

Claims 22-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kimura et al (1995) Biology of Reprod. 52, 709-720 in view of U.S. Patent 5,763,240 issued June 9, 1998 (Zarling et al).

Kimura et al teach the production of mice by the piezo-electropipette injection of sperm into mice ova to produce a zygote (page 711, col. 1, parag. 2, line 1 to page 712, col. 1, parag. 2). The zygote would obviously develop into progeny once transferred to a surrogate mouse. Kimura et al do not teach

the production of transgenic mice by injecting with the sperm targeting polynucleotides and a recombinase. Zarling et al teaches the production of transformed cells in culture by a method where DNA segments that are homologous to a target sequence, but contain a mutation of interested are first coated with a recombinase and second introduced to the target cell (col. 5, lines 54-63). Zarling et al teach that E. coli RecA or a recA-like protein can be the recombinases used to coat the targeting nucleotides (col. 11, lines 54-57). Rad51 is a mammalian function equivalent of RecA and known in the art at the time of filing. Thus at the time of filing, it would have been obvious to the ordinary artisan to modify chromosomal DNA in an oocyte or a sperm comprising injecting into an oocyte a composition comprising sperm and targeting polynucleotides coated with a recombinase. Further, the use of intracytoplasmic sperm injection for fertilization was well known and established in the art, as were the treatment of sperm by freezing drying, detergents and methods that removed sperm membranes.

Claims 38 and 40 are free of the prior art. At the time of filing, the art did not teach or suggest methods of altering the nucleic acid sequence of mitochondria by any methodology much less the methodology claimed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is (703) 308-1126. The examiner's SPE is Karen Hauda, whose telephone number is (703) 305-6608.

Any inquiry of a general nature or relating to the status of this application should be directed to the Art Unit Patent Analyst, Kay Pinkney, whose telephone number is (703) 305-3553.

The fax number is (703) 308-4242.

Deborah Crouch

DEBORAH CROUCH
PRIMARY EXAMINER
GROUP 1800/1630

Dr. D. Crouch
February 3, 2001